REMARKS

1. Pending Claims

Applicants acknowledge that claims 1, 2, 6, 7 and 14 are currently pending in the application, with claims 1 and 14 being in independent format. Applicants have added claims 15-21.

Applicants have added claims to more completely define the present invention. Claim 15 is dependent from claim 1 and specifies the one or more compounds are administered in a sequential or concurrent combination with flt3-ligand. Claim 16 is dependent from claim 2 and specifies the CD40 binding protein, antibody reactive with 4-1BB, 4-1BB-L, interferon alpha, RANKL, CD30 ligand antagonists, GM-CSF, IL-4, TNF-α, IL-3, c-kit ligand, and fusions of GM-CSF and IL-3 are administered in a sequential or concurrent combination with flt3-ligand. Claim 17 is dependent from claim 14 and specifies the additional step comprising administering one or more of the molecules selected from the group consisting of GM-CSF, IL-4, TNF-α, IL-3, c-kit ligand, and fusions of GM-CSF and IL-3. Support for claims 15-17 may be found at page 5, lines 19-27 in the application as originally filed.

Applicants have added several claims dependent on claim 6: claim 18 is drawn to a method for reducing tumor growth in a patient; claim 19 is drawn to a method for reducing tumor incidence in a patient; and, claim 20 is drawn to a method of increasing tumor rejection in a patient. Support for claims 18, 19 and 20 may be found in Examples 4, 5 and 6 at pages 23-30. Claim 21 is drawn to a method of inducing expression of IL-12 in tumors in a patient comprising the step of administering flt3-ligand and CD40 binding protein to the patient. Support for claim 21 may be found in Example 4, page 26, lines 2-4. Applicants urge that the claimed subject matter is fully supported by the specification as originally filed and does not constitute new matter.

2. Priority Dates

The Examiner states that all pending claims do not enjoy the benefit under 35 U.S.C. §120 of the parent filing dates. Applicants offer the following clarification of priority dates for the different elements of the claims. Applicants disclosed methods of augmenting an immune response by administering flt3-ligand in combination with CD40 binding proteins, antibodies reactive with 4-1BB and 4-1BB-L for the first time in U.S. Patent Serial No. 09/154,903 (now abandoned). Support in the specification as originally filed may be found, for example, at page 10 line 30 to page 12, line 4, as well as Examples 4 and 5. The '903 application has a filing date of September 17, 1998, and therefore aspects of claims 1, 2, 6, 7

and 14 pertaining to the use of flt3-L in combination with those compounds enjoy a priority date of September 17, 1998. A copy of the '903 application is enclosed for the Examiner's convenience. The remaining compounds used in combination therapy with flt3-l, namely INF-α, RANKL and CD30 ligand antagonists, were disclosed for the first time in the present application and therefore have a priority date of November 19, 1999.

3. Cross Reference to Related Applications.

The section describing reference to related applications has been rewritten to update the status of previously filed applications. In short, the three parent applications have been abandoned.

4. Title of the Invention.

The title has been amended to properly reflect the claimed invention. The new title is the USE OF FLT3-LIGAND IN COMBINATION THERAPY TO AUGMENT IMMUNE RESPONSES.

5. Abstract of the Disclosure.

The abstract has been amended to more precisely describe the claimed invention.

6. Trademarks designations.

Applicants have reviewed the subject application and believe all trademark designations have been made.

7, 8. 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 2, 6, 7 and 14 under 35 U.S.C. §103(a) as being unpatentable over *Lyman* (USPN 5,843,423) and/or *Brasel* (WO 97/12633) and/or *Fichelson* (Eur. Cytokine Netw) in view of *Kishida* (USPN 5,846,928) and/or *Cummins* (USPN 5,017,371) and/or *Srivastava* (USPN 6,017,544).

Applicants note that the §103(a) rejection only pertains to aspects of the claimed methods whereby flt3-ligand is used in combination with interferon alpha. Therefore, Applicants acknowledge that the presently claimed methods pertaining to CD40 binding protein, antibodies reactive with 4-1BB, 4-1BB-Ligand, RANKL and CD30 ligand antagonists are novel, nonobvious and free of any art.

Applicants respectfully submit the cited prior art does not provide the requisite suggestion, teaching or motivation to modify or combine the cited references. As a result, the burden of proving *prima facie* obviousness under the *Graham* analysis has not been satisfied.

Lyman teaches methods of using flt3-ligand alone or in combination with one or more cytokines, such as GM-CSF, for stimulating the proliferation of hematopoietic stem or progenitor cells. *Lyman* also discloses that this particular form of therapy may be used in the treatment of cancers. *Lyman* does not disclose or suggest the use of flt3-ligand in combination interferon alpha to augment immune responses in a patient.

Brasel builds upon the teachings of *Lyman* and further discloses methods of using flt3-ligand alone or in combination with one or more cytokines or growth factors (GM-CSF, IL-3, IL-4, TNF-α, c-kit ligand) for stimulating the proliferation of hematopoietic stem or progenitor cells to mobilize dendritic cells *in vivo*, as well as for *ex vivo* expansion. *Brasel* also discloses that administering flt3-ligand alone is effective in augmenting anti-tumor immune responses. *Brasel* does not disclose or suggest the use of flt3-ligand in combination with interferon alpha to augment immune responses in a patient.

Fichelson is a review article on flt3-ligand. The most pertinent part of *Fichelson* summarizes the findings described above for *Lyman* and *Brasel*, i.e., the regeneration and mobilization of hematopoietic stem cells, the amplification and activation of dendritic cells and induction of *in vivo* anti-tumor responses. *Fichelson* also discloses the use of G-CSF in combination with flt3-ligand to stimulate progenitor cells in the peripheral blood. *Fichelson* does not disclose or suggest the use of flt3-ligand in combination with interferon alpha to augment immune responses in a patient.

Kishida discloses an *ex vivo* method of activating NK cells by *in vitro* exposure to IFN-α. In *Kishida,* leukopheresis is performed on a patient and IFN-α is added to the collected cells. After short exposure, the lymphocytes are returned to the patient. The interferon-activated-NK-lymphocyte therapy may be used in the treatment of cancer. *Kishida* does not disclose *in vivo* administration of IFN-α to a patient.

Cummins describes a method for reducing the side effects of cancer therapy. Specifically, interferon is administered orally in a form adapted to promote contact with the patient's oral and pharyngeal mucosa in amounts effective to reduce the toxic side effects of chemotherapy and radiation therapy. *Cummins* does not teach methods of augmenting immune responses or methods of treating cancer.

Srivastava is not prior art. *Srivastava* has an issue date of January 25, 2000. As described above, the claims of the present invention enjoy the benefit of a filing date of

November 19, 1999 or an earliest effective filing date of September 17, 1998 depending on the particular combination therapy. Thus, *Srivastava* cannot be considered prior art because *Srivastava's* issue date is well after the present application's filing date(s).

The present invention is readily distinguished from the prior art. Applicants note that in determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). When viewing the invention as a whole, *Lyman* teaches that flt3-ligand is useful for stimulating the proliferation of hematopoietic stem or progenitor cells, and that flt3-ligand in combination with growth factors, such as GM-CSF, provides synergistic effects on proliferation. The use of additional growth factors is meant to further influence the maturation or effector function of the proliferating hematopoietic stem or progenitor cells. This is described in the *Lyman* reference at column 6, lines 42-49, which states "[o]ptionally, one or more cytokines selected from the group listed above can be combined with flt3-L to aid in the proliferation of particular hematopoietic cell types or affect cell function of the resulting proliferated hematopoietic cell population."

The present invention represents a significant advancement in the art that extends beyond the teachings of *Lyman/Brasel/Fichelson*. The presently claimed methods are founded upon the discovery that the use of flt3-ligand in combination with CD40 binding protein, antibodies reactive with 4-1BB, 4-1BB-Ligand, interferon alpha, RANKL and/or CD30 ligand antagonists serves to augment immune responses in a surprisingly strong manner. Notably, some of these compounds are meant to influence not only the proliferating hematopoietic cell population, but also additional cell types of the immune system, such as T- and B-cells. As demonstrated in Examples 4-6, this unique approach yields surprising results in augmenting host immune responses, which is especially evident in treating cancer. This unique insight and approach is not taught or suggested in the prior art references, alone or in any combination. Applicants respectfully submit the inventors of the presently claimed invention should be rewarded for their pioneering work and advancement in the art.

With regards to *Lyman/Brasel/Fichelson* in view of *Kishida*, Applicants note that the combined references do not render the presently claimed invention obvious. *Kishida* must be viewed as a whole, and does not teach administering IFN-α to the patient. *Kishida* discloses an *ex vivo* interferon-activated-NK-lymphocyte therapy that may be used in the treatment of cancer. There is no suggestion or teaching in *Lyman/Brasel/Fichelson* to use the *ex vivo*

interferon-activated-NK-lymphocyte therapy of *Kishida* or vice versa. Nothing in *Kishida* suggests the *in vivo* use of IFN-α. In fact, none of the references provide the theoretical underpinnings to motivate one of skill in the art to combine the two disparate therapies. Applicant's claimed method has nothing to do with *ex vivo* interferon-activated-NK-lymphocyte therapy. Applicants note that "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Applicants respectfully submit the combined references do not meet the requisite standard for establishing prima facie obviousness.

With regards to *Lyman/Brasel/Fichelson* in view of *Cummins*, Applicants believe the combined references do not meet the legal standard for establishing prima facie obviousness. Applicants further note that if a "proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). When viewed as a whole, the intended purpose of *Cummins* is to alleviate the toxic side effects of chemotherapy or radiation therapy to the oral and pharyngeal mucosa - nothing more. To modify *Cummins* into a method of augmenting an immune response that may be used to treat cancer would render *Cummins* unsatisfactory for its intended purpose, which is solely to alleviate side effects of chemo and radiation therapy. In addition, Applicants note that the cited references provide no motivation to use the method of *Cummins* in combination therapy with flt3-ligand to augment immune responses. Even if one of skill in the art did use flt3-ligand in combination with the methods of *Cummins*, there is not a reasonable expectation of successfully achieving the striking results reported by Applicants. Applicants respectfully submit the combination of *Lyman/Brasel/Fichelson* in view of *Cummins* does not establish a prima facie case of obviousness for the presently claimed invention, and as such, the rejection under 35 U.S.C. §103(a) should be properly withdrawn.

Because *Srivastava* is not prior art, the obviousness rejection of claim 14, which is drawn to enhancing a mammal's immune response to a vaccine antigen, cannot stand. Therefore, claim 14 is free of the art and in condition for allowance.

Applicants have demonstrated that the cited prior art does not meet the requisite standard for establishing prima facie obviousness for the claimed invention. Applicants further note that "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any

claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). As a result, all pending claims are in condition for allowance.

Reconsideration and allowance of pending claims 1, 2, 6, 7 and 14, as well consideration of newly added claims 15-21 is kindly requested.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Date: October 19, 2001 Signed: Nanci M. Kertson
Nanci M. Kertson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: David H. Lynch, Luis Borges, Robert E. Miller and Charles R. Maliszewski

Docket No.: 2836-C

Group Art Unit: 1644

Serial No: 09/444,027

Examiner: P. Gambel

Filed: November 19, 1999

For: DENDRITIC CELL STIMULATORY FACTOR

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The title has been amended as follows:

USE OF FLT3-LIGAND IN COMBINATION THERAPY TO AUGMENT IMMUNE RESPONSES ~~DENDRITIC CELL STIMULATORY FACTOR~~

The paragraph at page 1 under the heading "Related Applications' has been amended as follows:

This application is a continuation-in-part of U.S. Application Serial No. 09/154,903, filed September 17, 1998, now abandoned~~pending~~, which is a continuation-in-part of U.S. Application Serial No. 08/725,540, filed October 3, 1996, now abandoned~~pending~~, which is continuation-in-part of U.S. Application Serial No. 08/539,142, filed October 4, 1995, now abandoned~~pending~~.

The Abstract of the Disclosure has been amended as follows:

Flt3-ligand ~~can be used~~has been shown to generate large numbers of dendritic cells from hematopoietic progenitor and stem cells. In this regard, ~~F~~flt3-ligand can be used to augment immune responses to cancerous and neoplastic disease when ~~in vivo, and expand dendritic cells ex vivo. Such dendritic cells can then be used to present tumor, viral or other antigens to naive T cells, can be useful as vaccine adjuvants. When flt3 L is used and/or~~ administered in combination with other reactive agents, e.g. CD40 binding proteins, 4-1BBL or antibodies reactive with 4-1BB, CD30 ligand antagonists, RANKL, and/or interferon alpha. Such combination therapy may also be used to enhance immune responses to vaccine

antigens. ~~the combination further enhances immune responses and the effectiveness of vaccine adjuvants.~~